Attorney Docket No. 62041 (51588)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Elmaleh, *et al.*

Application No.: 10/827,054 Confirmation No.: 2370

Filed: April 19, 2004 Art Unit: 1618

For: *METHOD FOR MONITORING BLOOD FLOW AND METABOLIC UPTAKE IN TISSUE WITH RADIOLABELED ALKANOIC ACID* Examiner: Melissa J. Perreira

DECLARATION UNDER 37 CFR 1.132 OF DAVID ELMALEH, PH.D.

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The undersigned, David Elmaleh, declares as follows:

1. I am a named inventor of the above-referenced patent application ("the Application"). I have a Ph.D. degree in Organic Chemistry from Hebrew University, Jerusalem, Israel. I am currently an Associate Professor of Radiology at Harvard Medical School and the Director of Contrast Media Chemistry at the Massachusetts General Hospital in Boston, an affiliate of the assignee of the present application. I have about 30 years of experience in research in Medicinal Chemistry and Radiopharmaceutical Development of research, including diagnostic imaging agents for PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computerized Tomography).

2. I have reviewed the Application and the final Office Action issued from the U.S. Patent Office on May 22, 2007 ("the Office Action"). I understand that all pending

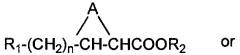
claims of the application have been rejected as unpatentable over a combination of references (PCT Patent Publication No. WO 97/19705 to Elmaleh ("Elmaleh"), in view of United States Patent Nos. 4,323,547 to Knust, *et al.* ("Knust") and 4,524,059 to Elmaleh ("US-Elmaleh")). I am listed as an inventor on the two Elmaleh patents/applications cited by the Examiner.

3. The compounds of the claims of the present Application differ from the compounds of the Elmaleh PCT application, the Knust patent, and the Elmaleh patent. For example, the compounds of claim 1 of the Application are represented by the following structure:

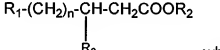
$$R\text{-}(CH_2)_n\text{-}Z\text{-}(CH_2)_mCO_2H,$$

in which n is 8-22, m is 1-10, R is a CH_3, aryl or a heterocyclic group, and Z is a cyclic or heterocyclic organic substituent which causes said analog to be metabolically trapped in said tissue. The compounds further include a radioactive isotope that is bonded to a carbon atom of the analog.

4. In contrast, the Elmaleh PCT application discloses compounds according to the structures



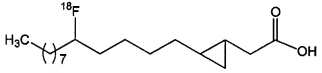
or



, while Knust discloses fatty acids labeled with radioactive isotopes, in particular [^{18}F]-fluoroheptadecanoic acid, and their use in methods of investigating the kinetics of myocardial metabolism, and the Elmaleh U.S. Patent discloses a radioactively labeled analog of a fatty acid having an organic substituent bound at the C3, C5, C7 or C9 positions counting from the carboxyl carbon atom, and the analog is capable of being taken up by mammalian tissue and exhibiting an in vivo beta-oxidation rate below that of a corresponding radioactively labeled fatty acid.

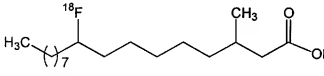
5. The utility of myocardial imaging agents is affected by the uptake of the imaging agent in heart, blood, liver and lung. Therefore, the usefulness of an agent (such as a labelled fatty acid) will affected by the heart-to-tissue uptake ratio of the agent. In general, the higher the heart-to-tissue ratios, the more selective the agent is for myocardial tissue.

6. The compounds of the Application have unexpectedly superior properties compared to the compounds of the cited references. For example, the present Application discloses and claims the compound [^{18}F]-9-fluoro-3,4-cyclopropylheptadecanoic acid (see, e.g., claim 147), represented by the structure:



This compound, hereinafter referred to as [^{18}F]FCPHA, has a cyclopropyl ring located at the 3,4-position (that is, the cyclopropyl moiety includes carbon atoms 3 and 4 of the fatty acid chain).

The Elmaleh references cited by the Examiner contemplate certain labeled β-methyl-substituted fatty acids. An example of such a compound is [^{18}F]-9-fluoro-3-methylheptadecanoic acid, hereinafter referred to as [^{18}F]FBMHA, represented by the structure:



The only difference between [^{18}F]FCPHA and [^{18}F]FBMHA is the presence of a 3,4-cyclopropyl group in [^{18}F]FCPHA rather than a 3-methyl group in [^{18}F]FBMHA.

7. Certain experiments were performed to compare the properties of [^{18}F]FCPHA and [^{18}F]FBMHA. The compounds were administered intravenously to rats, and the biodistribution of the compounds at 5 and 60 min after intravenous

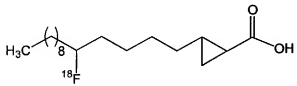
administration was measured. The results are summarized in Table 1, which presents the heart-to-tissue ratios for the two compounds at the specified times.

Table 1: Heart-to-Tissue Ratios for [^{18}F]FCPHA and [^{18}F]FBMHA

RATIO	TRACER			
	[^{18}F]FCPHA		[^{18}F]FBMHA	
	5 min.	60 min.	5 min.	60 min.
Heart/Lung	3.3	4.6	2.0	2.9
Heart/Blood	25.8	20.4	2.6	2.9
Heart/Muscle	6.2	14.3	3.9	4.1
Heart/Liver	1.6	1.6	0.3	0.4

8. It can be seen from the results described in Paragraph 7 that the heart-to-tissue ratios for the two compounds are significantly different. In particular, the heart-to-blood ratio for the compound of the present claims ([^{18}F]FCPHA) is much higher than the corresponding ratio for [^{18}F]FBMHA (about 10-fold at 5 minutes, and more than 6-fold at 60 minutes). This is important because the diagnostic capability of an imaging agent (such as a cardiac imaging agent) can be improved by improving the target-to-non-target tissue ratio.

9. In a similar manner, experiments were performed to test the corresponding 2,3-cyclopropyl fatty acid [^{18}F]-8-fluoro-2,3-cyclopropylheptadecanoic acid (2,3-CP-8-[^{18}F]-FA) (a compound related to the generic disclosure of the Elmaleh PCT application as described above), represented by the structure:



The only difference between [^{18}F]FCPHA and the 2,3-cyclopropyl analog is the presence of a 3,4-cyclopropyl group in [^{18}F]FCPHA rather than a 2,3- cyclopropyl group

in 2,3-CP-8-[^{18}F]-FA, and the radiolabel is on the 8-carbon in 2,3-CP-8-[^{18}F]-FA rather than the 9-carbon in [^{18}F]FCPHA. It will be appreciated that the F-18 radiolabel (at C-8) of 2,3-CP-8-[^{18}F]-FA is at the same distance from the cyclopropyl group (5 carbon atoms) as the F-18 radiolabel on [^{18}F]-9-fluoro-3,4-cyclopropylheptadecanoic acid ([^{18}F]FCPHA) and the methyl analog described above (^{18}F]FBMHA). It was important to keep the distance between the cyclopropyl group and the radiolabel. The position of the radiolabel bond will have a lesser effect on uptake and metabolism because the C-F bond size as comparatively close to the size of the C-H bond. Apparently, the primary and more important cause for changes in metabolic activity of the analogs (e.g., as discussed herein) is the position of the cyclopropyl group relative to the –COOH group.

The results are summarized in Tables 2 (showing uptake of the 2,3-cyclopropyl compound) and 3 (which presents the heart-to-tissue ratios for the 2,3-cyclopropyl compound at the specified times).

Table 2: Uptake of 2,3-CP-8-[^{18}F]-FA

Uptake, % dose per gram

	5 min.	30 min.	60 min.
Heart	**1.24 ± 0.26**	**0.94 ± 0.14**	**0.96 ± 0.11**
Blood	**0.59 ± 0.14**	**0.34 ± 0.06**	**0.28 ± 0.11**
Liver	**4.25 ± 0.48**	**1.62 ± 0.26**	**1.46 ± 0.36**
Lung	**0.64 ±0.15**	**0.29 ± 0.03**	**0.33 ± 0.07**

Table 3: Heart-to-Tissue Ratios for 2,3-CP-8-[^{18}F]-FA

RATIO	2,3-CP-8-[^{18}F]-FA		
	5 min.	30 min.	60 min.
Heart/Blood	2.1	2.76	3.43
Heart/Liver	0.29	0.58	0.66
Heart/Lung	1.94	3.24	2.91

10. It can be seen from the results described in Paragraph 9 that the uptake of 2,3-CP-8-[^{18}F]-FA into heart is poor compared to uptake into liver. Comparison of the results in Table 1 with the results of Table 3 show that the heart-to-blood ratio for the compound of the present invention ([^{18}F]FCPHA) is much higher than the corresponding ratio for 2,3-CP-8-[^{18}F]-FA (about 12-fold at 5 minutes, and more than 5-fold at 60 minutes). This means that the present compound has increased myocardial uptake and kinetics. Again, this is important because a compound having a higher heart-to-blood ratio and/or higher heart-to-liver ratio and/or higher heart-to-lung ratio will have increased tissue selectivity and improved heart image resolution and diagnostic accuracy.

11. In my opinion, based on the results set forth in Paragraphs 7-10 above, it is unexpected and surprising that a compound of the present invention has higher heart-to-tissue ratios than the compounds described above corresponding to the references cited by the Examiner. I would expect this improved tissue selectivity to result in increased heart resolution and diagnostic accuracy.

12. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. 1001), and that such willful false statements may jeopardize the validity of the above-identified Application or any patent issued thereon.

Date: November 20, 2007

David Elmaleh, Ph.D.